Neuropsychopharmacological mechanisms of stimulant drug action in attention-deficit hyperactivity disorder: a review and integration

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Abstract

The psychostimulants, D-amphetamine (D-AMP) and methylphenidate (MPH), are widely used to treat attention-deficit hyperactivity disorder (ADHD) in both children and adults. The purpose of this paper is to integrate results of basic and clinical research with stimulants in order to enhance understanding of the neuropharmacological mechanisms of therapeutic action of these drugs. Neurochemical, neurophysiological and neuroimaging studies in animals reveal that the facilitative effects of stimulants on locomotor activity, reinforcement processes, and rate-dependency are mediated by dopaminergic effects at the nucleus accumbens, whereas effects on delayed responding and working memory are mediated by noradrenergic afferents from the locus coeruleus (LC) to prefrontal cortex (PFC). Enhancing effects of the stimulants on attention and stimulus control of behavior are mediated by both dopaminergic and noradrenergic systems. In humans, stimulants appear to exert rate-dependent effects on activity levels, and primarily enhance the motor output, rather than stimulus evaluation stages of information-processing. Similarity of response of individuals with and without ADHD suggests that the stimulants do not target a specific neurobiological deficit in ADHD, but rather exert compensatory effects. Integration of evidence from pre-clinical and clinical research suggests that these effects may involve stimulation of pre-synaptic inhibitory autoreceptors, resulting in reduced activity in dopaminergic and noradrenergic pathways. The implications of these and other hypotheses for further pre-clinical and clinical research are discussed. © 1998 Elsevier Science B.V. All rights reserved.

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1. Introduction

Nearly 60 years ago, Charles Bradley [15] made the first observation that benzedrine (a racemic mixture of D- and L-amphetamine) had a distinct calming effect on the behavior of hyperactive children. Since that time, a plethora of studies have attested to the effectiveness of the psychostimulants in alleviating the cardinal symptoms of attention-deficit hyperactivity disorder (ADHD) and these drugs are now widely used to treat it. Relatively little substantive progress, however, has been made in delineating the therapeutic mechanisms of

action of these drugs, although several well-developed hypotheses have been proffered [152,177,227,231,288].

Contrasting with a relative dearth of specific knowledge concerning the clinical mechanisms of action of stimulants are significant advances in the past 10 years in the pre-clinical neuropsychopharmacology of these drugs. New techniques such as microdialysis, which permits measurement of neurotransmitter levels in awake, behaving animals, as well as the development of many new drugs with effects on specific receptor subtypes, offer the potential of identifying the neurotransmitter systems and specific receptors which mediate the observed effects of stimulants in animals in multiple domains of behavior. At the same time, more sophisti-

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cated genetic, neuroimaging, neuropsychological and behavioral studies in clinical populations have provided important clues as to underlying aberrant neurobiological processes which may be altered by clinically effective drugs. The purpose of this paper is to review recent developments in each of these areas, premised on the belief that the integration of these results will lead to generation of more precise, testable hypotheses concerning clinical mechanisms of stimulant drug action in patients with ADHD.

The first section will summarize research concerning drug effects in ADHD and will serve to constrain and guide our attention to drug studies in animals which are relevant to the phenomena seen clinically. This section will be followed by segments devoted to: the basic neuropharmacology of amphetamine and methylphenidate (MPH); the psychopharmacology of stimulant effects with respect to locomotor activity, reward processes, rate-dependency, and cognitive processes, including learning, attention, and memory; genetic studies; neuroimaging studies; animal models of ADHD; and comparison between stimulant and non-stimulant drug effects in ADHD. Within each subsection, effects in animal and human subjects will be presented. The final section will be devoted to an integration of these results, with discussion of hypotheses concerning specific sites and mechanisms of action and implications for future pre-clinical and clinical research.

Of the three psychostimulants used to treat ADHD—D-amphetamine (D-AMP), MPH, and pemoline—the first two are by far the most widely prescribed and have been the focus of the most pre-clinical and clinical research. Therefore, this review will be limited to studies of D-AMP and MPH.

2. Clinical pharmacology of stimulants

ADHD is characterized by three major symptom clusters—inattentiveness, impulsivity and hyperactivity—which are differentially present in the three subtypes of the disorder recognized in the DSM-IV [1]. Numerous well-controlled studies have shown that the most widely used stimulants, D-AMP (Dexedrine), and MPH (Ritalin), are highly effective in alleviating all three clusters of symptoms assessed on the basis of parent and teacher behavior rating scales, direct observations in natural settings, and laboratory tests purporting to measure the constructs in question [85,231]. The clinically effective dose range in children is 0.2–0.5 mg/kg for D-AMP and 0.3–1.0 mg/kg for MPH. In the effective dose range, the impact on behavior is apparent within 2 h of administration, indicating that it is not mediated by long-term changes in receptor sensitivity.

Controlled outpatient stimulant trials have yielded an average response rate to a given stimulant of approximately 75% [9]. A pivotal study conducted at NIMH indicated that when drug dosage was carefully titrated against behavioral response in a day hospital setting, however, 98% of the sample of 48 children with ADHD exhibited a clinically meaningful response to one or the other stimulant [61]. Whereas the group data in this and other studies have not revealed significant differences between D-AMP and MPH in therapeutic or side-effect profiles [14,61,62], this study suggested that as many as 25% of individuals may respond to only one of the two stimulants [61].

Although treatment duration is usually at least several years in childhood and may extend into adolescence, there are no systematic reports of development of drug tolerance, nor is there evidence of differences between the effects of acute and chronic stimulant drug administration on specific behaviors.

It was long believed that the response to stimulants of children with ADHD was 'paradoxical' in that normal individuals were expected to exhibit an activating response. It is now accepted, albeit on the basis of a single study with D-AMP conducted at NIMH [187], that, at comparable doses, the responses of normal and ADHD children and normal adults to the psychostimulants are qualitatively similar and include reductions in activity level and impulsivity, as well as enhancement of attention-related processes.

Clinical research has revealed that ADHD occurs at greater than expected frequencies with numerous other conditions, including learning disabilities, oppositional defiant disorder, conduct disorder, depression, and anxiety disorders [159], suggesting the existence of multiple subtypes of ADHD which may differ in response to stimulant drug treatment. With the exception of several recent investigations suggesting reduced effectiveness of MPH in children with ADHD and co-morbid anxiety [60,138,176,255], these co-morbid subtypes are largely unstudied, however, and hence will not be considered further in this paper.

3. Neuropharmacology of stimulants

In order to understand the nature of the effects of D-AMP on catecholaminergic function, it is necessary to have some understanding of the anatomic distribution and functional characteristics of the dopaminergic and noradrenergic neurotransmitter systems.

3.1. Neuroanatomy and neurophysiology of dopamine and norepinephrine systems

The dopamine (DA) system consists of two primary ascending subsystems: (a) the nigrostriatal system origi-

nating in the A9 area of the substantia nigra and terminating in the striatum which consists of the caudate and putamen; and (b) the mesocorticolimbic pathway, which, in the rat, extends from the A10 neural group in the ventral tegmental nucleus in the midbrain to limbic structures, including the nucleus accumbens, olfactory tubercle, lateral septal nuclei and central amygdaloid nucleus, as well as to cortical sites, including the prefrontal cortices (PFCs) [206,265]. In the primate, dopaminergic projections from the midbrain innervate most of the cortical mantle [178].

In contrast to the DA system which innervates discrete brain structures, the norepinephrine (NE) system has terminals throughout the brain and thereby exerts more widespread regulatory effects. The primary NE pathway is the dorsal noradrenergic bundle, which originates in the locus coeruleus (LC) and projects rostrally to the medial forebrain bundle and the limbic system including the hippocampus, amygdala, septum and anterior olfactory cortex [127]. The ventral noradrenergic bundle arises in nuclei A1 through A5 in the rostral medulla oblongata and projects via the lateral tegmental tract primarily to the hypothalamic and peri-hypothalamic areas. Noradrenergic projections extend throughout the cortex and are particularly dense in the frontal cortex and cingulate gyrus [63].

Five DA receptor subtypes have been identified and grouped into two subfamilies: the D-1-type receptors (consisting of subtypes D-1 and D-5), and the D-2-like subfamily (comprising types D-2, D-3, and D-4) [35]. The D-1 and D-2 receptors are present in all dopaminoceptive regions of the rat brain, with particularly high concentrations in the caudate-putamen, nucleus accumbens and olfactory tubercle, whereas D-3 and D-4 subtypes are more selectively associated with limbic regions. In the primate, D-4 receptors are also found in the PFC. The D-5 subtype is limited to the hippocampus, hypothalamus, and the parafascicular nucleus of the thalamus in the rat [35], but is found in significant numbers in primate cortex. DA is an effective agonist at all DA receptor subtypes.

In addition to post-synaptic receptors, inhibitory autoreceptors are present on the soma and dendrites as well as axon terminals of pre-synaptic dopaminergic neurons [26] in both the nigrostriatal [115] and mesocortical [252] pathways in rats. In humans, somatodendritic autoreceptors were not found on mesocortical DA neurons in a recent study; axonal autoreceptors (which include those in the synapse) were not examined [156]. DA autoreceptors appear to be primarily of the D-2 type, and function as part of a feedback mechanism wherein stimulation by DA or other agonists results in decreased membrane excitability, as well as decreased synthesis and release of DA, whereas DA antagonists have the opposite effects [34,206]. Autoreceptors appear to be qualitatively identical to post-synaptic receptors but are 3–10-fold more sensitive, responding at lower doses of DA and DA agonists [229,283].

Three families of noradrenergic receptors have been described—α-1, α-2, and β (each of which also have subtypes). Both α-1 and β receptors are thought to exist primarily at post-synaptic sites, whereas α-2 receptors occur both pre- and post-synaptically. Stimulation of pre-synaptic α-2 autoreceptors inhibits neurally mediated release of NE. Stimulation of pre-synaptic β-2 adrenergic receptors, however, is associated with modest enhancement of NE release. [96].

D-AMP and MPH are termed indirect agonists in that they do not stimulate catecholaminergic receptors directly, but rather facilitate the action of DA and NE. This is accomplished via three mechanisms: inhibition of reuptake, facilitation of release into the synaptic cleft, and inhibition of the catabolic activity of monoamine oxidase (MAO) [70,90]. D-AMP produces the first two of these effects by binding to the (pre-synaptic) DA transporter, inducing a reverse transport process [7,237]. Recent evidence indicates that MPH blocks DA re-uptake by binding to the DA transporter, but does not act as a substrate [237]. An additional noteworthy difference between the stimulants is that MPH releases DA from reserpine-sensitive storage pools, whereas D-AMP facilitates release of DA from newly synthesized stores [38].

At very low doses, beginning at 0.25 mg/kg, amphetamine has been shown to stimulate pre-synaptic inhibitory dopaminergic autoreceptors in both the nigrostriatal and ventral tegmental areas (VTAs) [17,18,90,91], resulting in an inhibition of firing rate of these neurons. Desensitization of dopaminergic (A10) autoreceptors has been shown to occur following repeated high-dose (5 mg/kg) injections of D-AMP [283].

In addition to its effects on dopaminergic pathways, D-AMP (0.25–1.0 mg/kg) stimulates α-2 adrenergic autoreceptors, resulting in a profound inhibition of the spontaneous firing rate of LC neurons [84], mimicking that produced by clonidine [90] and similarly blocked by yohimbine, an α-adrenergic antagonist [64]. Furthermore, D-AMP produced an increase in the spontaneous firing rate of hippocampal cells, which receive inhibitory input from the LC [104].

MPH has also been shown to produce a dose-dependent (0.4–1.1 mg/kg) reduction in firing comparable to that produced by clonidine [133,167]. A single dose was found to increase the affinity of α-1 and α-2 cortical adrenergic binding sites. Both acute and chronic treatments produced a down-regulation of α-1 but not α-2 receptors [147].

3.2. Functional neurophysiology of NE and DA systems

3.2.1. Norepinephrine

As originally described by Pribram and McGuinness [180] and elegantly elaborated by Tucker and Williamson [264], the dopaminergic and noradrenergic systems are specialized for different self-regulatory functions. Noradrenergic neurons are important in mediation of the orienting response, selective attention, and possibly vigilance. In a seminal study, Aston-Jones and Bloom [4] demonstrated that neurons originating in the LC of the rat responded selectively to novel environmental stimuli and that their activity diminished with stimulus repetition, corresponding to the psychophysiological phenomenon of habituation. Furthermore, other research in animals, reviewed by Foote [75] and Robbins [200] showed that noradrenergic stimulation increased the response to sensory stimulation, thereby enhancing the signal-to-noise ratio and serving to filter out irrelevant stimuli. Rats with genetically high levels of NE manifest high levels of exploratory behavior, as though failing to habituate to novel surroundings [118]. Studies by Robbins and colleagues [200] have shown that 6-OH-DA-induced lesions of the dorsal noradrenergic bundle produce deficits in the acquisition, though not performance, of conditional (but not simple) visual discrimination tasks, serial choice reaction time [25], and other tasks sensitive to selective or sustained attention, under very specific conditions [40].

The role of projections from the LC on tasks requiring selective and sustained attention was also demonstrated in studies by Aston-Jones, Rajkowski, and colleagues [5,6,185,186] using an 'oddball' paradigm, in which monkeys are trained to release a lever following a visual target cue (e.g. a horizontal line), occurring on 10–20% of trials, and to withhold responding to the non-target (e.g. a vertical line). Simultaneous electrophysiological recordings in normally alert monkeys indicated that LC neurons were selectively active in response to the target stimulus, as was the P300 response; reversing the target and non-target stimuli also reversed the LC and P300 responses to correspond to the (new) target and non-target stimuli. The frequency of these physiological responses paralleled the percentage of accurate behavioral responses on the task. Very high tonic levels of LC activity were associated with a hyperaroused, agitated behavioral state, a reduced frequency of behavioral response to the target, a higher frequency of false alarms (i.e. responses to the 'distractor') and an increased response of LC neurons to the distractor. Very low tonic LC activity, accompanied by drowsiness, was also associated with increased LC response to the distractor and poor performance.

In summary, performance in these studies was optimized at moderate levels of LC activity, as predicted by the Yerkes–Dodson ('inverted U') curve [286] relating performance to arousal. The task is similar in principle to the continuous performance test (CPT), described below, used in studies of vigilance in humans; the pattern of results in these animal studies suggests that a signal detection analysis would yield a reduction in d' (index of discrimination between target and non-target stimuli) at both high and low levels of LC activity.

The PFC, a termination region of LC neurons, is important in mediating working memory and inhibition of response to non-relevant stimuli. Studies by Arnsten, Goldman-Rakic and colleagues, recently reviewed by Arnsten [2], have shown that administration of the α-2 noradrenergic agonist clonidine to monkeys can reverse the negative effects of NE depletion due to ageing and neurotoxic lesions of the PFC, on delayed response and delayed alternation tasks. Studies with more selective α-1 and α-2 adrenergic agonists and antagonists have established that positive effects on these tasks in animal studies are specifically due to stimulation of α-2a receptors, and indicate a post-synaptic site of action. When administered to normal adult volunteers in a low dose of approximately 200 μg/70 kg, clonidine produced impairment in divided and focused attention [37,46], vigilance [45], working memory [44] and paired associate learning [76]. Similarly, adverse effects of low doses on working memory were observed in aged monkeys [3]. Studies in animals suggest that in this lower dose range, clonidine stimulates pre-synaptic autoreceptors [246]. There is also important evidence that impaired vigilance performance, seen at very high levels of LC activity as described above, can result from excessive NE release at α-1 receptors in the PFC [2].

It is important to note that DA also was found to play a role in modulating the function of the PFC in this series of studies. Spatial working memory was enhanced by infusion of D-1- or D-2-receptor agonists directly into the PFC and impaired by infusion of D-1 antagonists or low ('pre-synaptic') doses of D-1 agonists [2]. There appears to be a narrow 'window' of optimal DA stimulation, however, in that very high DA levels, such as those induced by stress or mimicked by infusion of a selective D-1-receptor agonist into the PFC impaired spatial working memory [2]. Other evidence suggests that D-2 and D-4 receptors may also mediate detrimental effects of excessive DA stimulation [2].

3.2.2. Dopamine

Whereas the NE system is primarily involved in mediating perceptual input processes, the DA system regulates motor output, as well as the response to reinforcement. Selective stimulation and lesion studies reveal that DA neurons in the nigrostriatal and mesolimbic pathways are essential for the selection, initiation, sequencing and maintenance of motor func-

tions [264]. In contrast to the 'habituation bias' exhibited by noradrenergic neurons, the dopaminergic systems display a 'redundancy bias,' in that activation of these systems increases redundancy of information in brain channels. Dopaminergic stimulation of PFC neurons was found to reduce the response of these neurons to novel stimuli, thereby diminishing the signal:noise ratio [259]. Redundancy serves to maintain a tonic readiness to respond, facilitates the completion of internally generated motor sequences, and, may in conjunction with reward mechanisms, promote the formation of stimulus–response associations.

Recent data also indicates that projections from frontal cortex to striatum play a role in regulating tonic DA activity. Grace [83] has recently expounded on cellular mechanisms wherein corticostriatal afferents stimulate pre-synaptic DA neurons to maintain a tonic low level of extracellular DA. This DA stimulates synthesis-modulating and release-modulating autoreceptors on the pre-synaptic DA terminal, thereby decreasing the amplitude of spike-dependent phasic DA release and dampening the acute effects of dopaminergic activation by stimulant drugs and other agents.

In summary, and retaining the terms introduced by Pribram and McGuinness [180] with respect to the neural regulation of cognition, the noradrenergic system regulates arousal and the mediation of phasic perceptual input processes, whereas the dopaminergic system is specialized for activation, mediating motor output function and tonic readiness to respond. Studies further suggest that these noradrenergic and dopaminergic functions are lateralized to the right and left hemispheres, respectively [264]. These general distinctions between the functions of DA and NE are tempered by the findings described above that DA also modulates the functioning of the PFC. Furthermore, other recent data reveals that DA may also function in a phasic manner as a learning signal to condition salient information [221].

4. Stimulant effects on locomotor activity

Careful studies using truncal actometers have shown that children with ADHD are more active than normal children during nearly all daytime activities as well as during sleep [182], and that D-AMP (15 mg/day or as tolerated, at 8:00) significantly decreased activity level throughout the day [181].

The effects of amphetamine on behavior in animals vary substantially with dosage. Studies have shown that DA agonists, including L-amphetamine [243], apomorphine [53,244] and L-dopa [53], at the very low doses which stimulate autoreceptors, produce a concomitant reduction in locomotor activity.

At moderately low doses (0.5–2.0 mg/kg), the primary effect of amphetamine in rats is to increase locomotor activity. Following high doses (2–10 mg/kg and greater), a short initial period of increased locomotor activity is followed by intensive stereotyped behavior, including repetitive gnawing, sniffing, licking, and rhythmic head movements [135,219]. The pattern with increasing dosage has been termed a 'motor stimulatory effect', wherein, as dose and rate increase, the organism tends to show increasing response rates within a decreasing number of response categories [146]. Extensive research has demonstrated that the facilitation of locomotor activity by amphetamine is primarily referable to post-synaptic stimulation of mesolimbic dopaminergic neurons whereas stereotypy is mediated by the nigrostriatal system [135]. Furthermore, a recent study provided evidence that the effects of a low dosage (0.4 mg/kg) of D-AMP in increasing locomotor activity were mediated by effects on D-1 receptors, whereas the marked increase in stereotypy and locomotor activity produced by a high dose (4 mg/kg) resulted from stimulation of both D-1 and D-2 receptors [71]. Single-unit recording has recently demonstrated that D-AMP (1.0 mg/kg s.c.) increased the firing rate of active motor neurons in freely moving rats while inhibiting the activity of non-motor neurons [95].

Paralleling results with D-AMP, MPH has also been shown to stimulate locomotor activity at relatively low doses (4–5 mg/kg) and to induce stereotypic behavior at higher doses (8 mg/kg and greater) [72,105,219]. Furthermore, Hughes and colleagues [105] reported that, independently of its effects on activity, MPH (8–16 mg/kg) produced a decrease in preference for novelty.

The effects of amphetamine and MPH appear to be modulated by serotonergic transmission in ways that are complex and as yet incompletely understood. Consistent with electrophysiological findings [197], stimulant dosages which produced stereotypies (30 mg/kg MPH and 1.0–5.0 mg/kg amphetamine) also increased levels of 5-HT in striatum and frontal cortex, areas which receive serotonergic projections from the dorsal raphe nucleus [131]. In contrast, levels of 5-HT were not increased by either drug in the hippocampus, which receives serotonergic input exclusively from the median raphe [131], suggesting D-AMP's effects are specific to dorsal raphe projections. Serotonergic modulation of amphetamine-induced locomotor activity may be enhancing or inhibiting depending on D-AMP dosage and the 5-HT receptor subtype studied [134,260].

A phenomenon described in animals and human amphetamine addicts, but which has not been investigated in ADHD, is behavioral 'sensitization' or 'reverse tolerance', in which repeated intermittent amphetamine administration enhances the organism's response to subsequent administration of the same dose. Sensitiza-

tion has been demonstrated for many amphetamine-induced behaviors [205], including locomotion, stereotypy, performance in a Y-maze, as well as amphetamine-induced disruption of selective attention [47]. One study, however, suggested sensitization may not occur for D-AMP effects on brain self-stimulation reward [284]. Sensitization has been produced in animal studies by doses less than 1.0 mg/kg [204], ranging up to 10 mg/kg., with typical injection frequencies of one or two times daily for 1–2 weeks [13,169]. Even a single D-AMP dosage has been shown to enhance response to a second dosage administered weeks later, with progressively greater enhancement seen following multiple doses [205]. A recent study reported that sensitization did not occur following MPH, but rather that MPH-induced increases in locomotor activity became smaller with repeated injections of 20 mg/kg [155], indicating tolerance.

5. Stimulant effects on reinforcement processes

5.1. Animals

Stimulant drugs have been shown to have rewarding properties in self-stimulation and conditioned reinforcement paradigms. Animals have been shown to self-administer D-AMP [102], and amphetamine produces increased responding for brain self-stimulation in dose-dependent fashion in the range of 0.25–1.0 mg/kg, i.p. [107]. Furthermore, D-AMP enhances the reward value of other stimuli. Numerous studies have shown that D-AMP enhances responding to a previously conditioned reinforcer (CR). This effect has been shown for i.p. amphetamine doses ranging between 0.5 and 2.0 mg/kg [151] and for intracranial injections of amphetamine directly into the nucleus accumbens at doses ranging from 3.0 to 20.0 µg [117,258]. It has also been shown that animals will prefer, when drug-free, a cue-distinct environment in which they previously experienced the maximal effects of amphetamine [240]—a phenomenon known as conditioned place preference.

The mesolimbic dopaminergic pathway from the VTA to the nucleus accumbens mediates these rewarding effects of amphetamine. Microdialysis has verified that amphetamine produces DA-enhancing effects in the nucleus accumbens [52,98,130]. Electrical stimulation of the VTA was found to mimic the stimulus properties of D-AMP [59]. In addition, selective lesions of the nucleus accumbens, produced by the neurotoxin 6-OH-DA, blocked amphetamine-enhancing effects on both self-administration [145] and on responding to a CR [258]. The pedunculopontine tegmental nucleus, which receives projections from the ventral pallidal complex, which in turn is innervated by the nucleus accumbens, is a critical neural substrate of the reinforc-

ing, but not the locomotor stimulatory effects, of amphetamine [113,166]. Other research implicates the basolateral amygdala, and the ventral subiculum—major limbic sources of afferents to the ventral striatum—in responding to a CR [20].

The reinforcing properties of D-AMP appear to be mediated by effects of DA on both D-1 and D-2 receptors, as suggested by the finding of a compensatory increase in amphetamine self-administration following addition of either a D-1- or a D-2-receptor antagonist [173]. Differences between D-AMP and MPH in mechanisms of reinforcing properties are suggested by the finding that haloperidol pre-treatment blocked place preference conditioning induced by D-AMP but not by MPH [160].

Other neurotransmitter systems may act to modulate amphetamine-mediated effects on reward. Ritz and Kuhar [199], for example, reported that the potency of amphetamine in operant self-administration studies was negatively correlated with 5-HT uptake inhibition by paroxetine. Fletcher [74] showed that amphetamine-enhanced responding for a CR was abolished by D-fenfluramine, a 5-HT-releaser and reuptake inhibitor. These studies suggest that serotonin activation may oppose the reinforcing effects of amphetamine. Involvement of the opiate system was suggested in the finding that naloxone, an opioid receptor antagonist, blocked amphetamine-induced place preference conditioning [262].

5.2. Humans

The impact of the stimulants on reward processes is of particular interest in that the behavioral aberrations in ADHD have been attributed to an elevated reward threshold [8,92], such that more frequent, more immediate, or more salient reinforcers are necessary to maintain appropriate responding. An alternate hypothesis of an abnormally increased responsiveness to immediate (as opposed to delayed) reinforcers has also been advanced [56,112]. Clinical research to date has not provided consistent support for either hypothesis [236].

Very few studies have addressed the effects of the psychostimulants on reward processes in individuals with ADHD. Wilkison and colleagues [285] reported that MPH increased the total number of button-presses produced by children with ADHD in order to obtain monetary reinforcement on a progressive ratio schedule (in which the criterion number of responses for a reward increases after each reward is dispensed). These results suggested that MPH increased the efficacy of the reinforcement, or alternately stated, reduced the reward threshold in these subjects. Pelham [171], however, reported that MPH reduced errors during learning of a spelling task irrespective of the concurrent reinforcement schedule (none, partial or continuous reinforce-

ment), providing no evidence of reward-mediated drug effects. Most recently, Solanto [236] compared the effects of MPH and tangible reinforcers on a CPT of attention and found evidence for differences in the mechanisms of action of these two interventions. Although both treatments improved the mean level of performance, only MPH reduced the deterioration in performance over time compared to placebo, suggesting effects of MPH but not exogenous reward on energetic 'effort' pools [215].

6. Rate-dependency

6.1. Animals

Rate-dependency refers to the observation that low baseline rates of response are increased by a drug whereas higher rates are found to increase to a lesser extent or to decrease as a result of drug treatment; response rate is thus an inverse function of baseline rate, as described in the model, $\log(D/C) = (a - b)\log(C)$, where D is response rate on drug, C is baseline response rate, and a and b are constants [51]. Many studies in a wide range of species, reviewed by Dews and Wenger [51] have documented rate-dependent effects of amphetamine on fixed-interval and fixed-ratio schedules of reinforcement. Such effects have been shown for amphetamine doses as low as 0.1 mg/kg, with doses between 0.3 and 1.0 mg/kg found to produce decreases in high base rate responding. Rate-dependent effects on spontaneous motor activity have been shown for doses ranging from 1.0 to 15.0 mg/kg of D-AMP [81] and for 0.8 mg/kg methamphetamine [68]. Thus, it appears that decreases in motor activity can be produced by amphetamines at doses lower than those which generate stereotypy and associated reduction in locomotor activity. Robbins and colleagues [202] showed that rate-dependent effects of amphetamine were attenuated by 6-OH-DA-induced depletion of catecholamines in the nucleus accumbens, indicating that the mesolimbic DA system is important in mediating these effects.

Two studies have investigated the extent to which MPH produces rate-dependent effects in animals. Sagvolden and colleagues [210] studied effects of six doses of MPH ranging from 1.0 to 15.0 mg/kg on a fixed interval (FI-60 s) schedule of reinforcement. FI schedules are useful for studying rate-dependency because the baseline pattern of response is a 'scallop', such that the rate of response is low early in the interval and increases toward the end of the interval; it is thus possible to observe drug effects on both high and low rate behaviors within the same animal. The results, however, provided minimal support for rate-dependent effects. The authors speculate that their findings of an

increased rate of reinforced responses early in the interval at low doses (6.0 and 9.0 mg/kg) were better explained as the result of a lengthened reinforcement gradient produced by MPH. By contrast, the reduced rates of reinforced responding seen later in the interval with lower doses and seen at all intervals with the highest doses (12.0 and 15.0 mg/kg) were attributed to the motor stimulatory effect of psychomotor stimulants, resulting in perseverative stereotyped responding.

Heyman [100] more recently postulated that rate-dependent effects can be derived from the matching law formulated by Herrnstein [99], which maintains that response rate is a negatively accelerated function of reinforcement rate. The author examined the effects of five doses of MPH, ranging from 0.5 to 8.0 mg/kg on seven different variable internal (VI) reinforcement schedules. Results demonstrated that, as predicted, response rate on MPH was a function of reinforcement efficacy, which was increased by the 1.0 and 2.0 mg/kg doses, and which accounted for 92% of the variance. However, it should be noted that the nature of this function is such that it can never generate actual decreases in response rate, and indeed none were found in this study. Thus, the applicability of these findings to the drug-induced reduction in activity level in ADHD may be limited.

6.2. Humans

Robbins and Sahakian [201] postulated that the decrease in spontaneous motor activity seen in children with ADHD after treatment with stimulant drugs is attributable to rate-dependent effects. Their re-analyses of raw data from several drug studies of ADHD children yielded a good fit with the rate-dependency equation. In particular, re-analysis of data from the NIMH study of drug effects on normal children, normal adults, and children with ADHD [188], yielded a slope of −0.65 for the curve of drug response rate as a function of base rate. Whereas both groups of children showed a decrease in activity on 0.5 mg/kg D-AMP, normal men, who had as a group much lower activity counts at baseline, showed a very small (but statistically significant) decrease only on the lower of two D-AMP doses (0.25 and 0.5 mg/kg) they received. Furthermore, the greatest reductions in activity were found for the most active ADHD children, whereas increases in activity were found for some normal adults within the group. A subsequent study by Solanto [232] of children with ADHD also reported a highly significant correlation of −0.94 between baseline spontaneous locomotor activity and the change in activity level following MPH administration.

The effect of MPH on schedule-induced operant responding in children with ADHD was examined in two studies. Weber [277] compared effects of MPH on

fixed ratio (FR) and differential reinforcement of low-rate responding (DRL) schedules, selected to generate high and low base rates of responding, respectively. The predicted rate-dependency effects were not found in that the drug increased the FR correct response rate in dose-dependent fashion, and had no effect on DRL response rate. Within the FR (but not the DRL) schedule, rate-dependency effects were found, however. Rapport et al [191] similarly reported that MPH increased the response rate on a high base-rate schedule (VR5) but had no effect on a low rate schedule (FI-30 s). Rate-dependent effects were found within each schedule.

It is important to note an inherent confound in the design of these studies in that a change in response rate is likely to have very different effects on rate of reinforcement on the two different schedules. On the ratio schedule, the rate of reinforced responses will increase with increased response rate. On the DRL and FI schedules, on the other hand, the reinforcement rate is likely to decrease or be unchanged with increased response rate (depending on the base rate of reinforcement relative to the maximal rate, which was not reported). Thus, if response rate on MPH is primarily a function of drug effects on reinforcement efficacy (rather than rate-dependency), one would expect that MPH would produce an increase in response rate on the ratio schedules but would decrease or have no effect on response rate on the DRL and FI schedules. These are precisely the results which are reported. That rate-dependent effects are also operative was suggested by the within-schedule results.

Mathematical difficulties with the rate-dependency model have been raised by Gonzalez and Byrd [82], who have pointed out the inherent dependency between D/C and C, which may yield spuriously high correlations. They advocate the following modification of the equation, which was not, however, utilized in any of the studies referenced above: $\log(D) = \log(a) + (b + 1)\log(C)$.

7. Stimulant effects on cognitive processes

7.1. Animals

7.1.1. Attention

Effects of D-AMP on 'attention' or stimulus control of behavior are assessed on tasks in which the animal must respond selectively to a cue (e.g. presentation of a light) which indicates which response alternative (e.g. left or right lever) will yield reinforcement. These tasks would appear to be analogous to choice reaction time tasks in humans, with the exception of the absence of an immediate reinforcer in the latter. Effects of D-AMP in rats in these studies are biphasic, with low doses

(0.25–0.50 mg/kg) increasing accuracy and reducing choice latency, and higher doses (1.0 mg/kg and greater) generally impairing performance [86–89,116,139]. Impairment of stimulus control of responding by D-AMP in rats was antagonized by 6-OH-DA lesions of nucleus accumbens, suggesting mediation by mesolimbic dopaminergic stimulation [203]. The low dose range for positive effects on attention suggests the possibility of mediation by autoreceptors.

7.1.2. Learning and memory

As summarized by McGaugh [153], pre-training injections of D-AMP in doses of 0.5–2.0 mg/kg have been found to enhance conditioned behavior on avoidance and discrimination tasks. Furthermore, numerous studies have now shown that D-AMP facilitates memory consolidation processes independently of effects on acquisition. Post-training injections of D-AMP (0.5–5.0 mg/kg) improved long-term retention of discrimination tasks [128], active avoidance tasks [67], as well as inhibitory (step-down passive avoidance) tasks [114]. An inverted U-shaped dose–response function on a passive avoidance task was reported by Haycock [97], wherein performance was improved by moderately low doses (0.3 and 1.0 mg/kg) but not by very low (0.03 or 0.10 mg/kg) or high (3.0 mg/kg) doses. Low post-training doses of D-AMP (0.25 and 0.33 mg/kg) were also found to improve performance on tasks involving trial-dependent ('working') memory, even at long retention intervals [168,245]. D-AMP also specifically facilitates retrieval processes following diverse sources of forgetting [184,216]. Low doses (0.25 or 0.5 mg/kg), but not higher doses, facilitated retrieval in rats following a 3-week training-to-test interval [216], whereas 2.0 mg/kg was effective in rats following a much longer (2.5 months) period [184].

Packard and White [168] demonstrated that post-training injections of 2.0 mg/kg D-AMP, or of a selective D-2-receptor agonist, but not of a selective D-1-receptor agonist, facilitated memory of two radial maze-learning tasks, suggesting D-2-receptor mediation of the D-AMP effects. One of the two tasks had previously been shown to be sensitive to nigrostriatal lesions, whereas the other had been shown to be dependent on a functional septo-hippocampal pathway, which receives dopaminergic input from the VTA; thus the involvement of both dopaminergic systems in D-AMP's effects is indicated in the results of this study.

7.2. Children with and without ADHD

7.2.1. Attention and inhibitory control

Laboratory studies have attempted to identify a deficit in a specific stage of information-processing or attentional domain in children with ADHD. Studies of

information-processing by Sergeant [223] and others have applied the additive factors method (AFM) to such measures as the Sternberg memory search task [241], on which the four major stages of information-processing can be delineated and their difficulty selectively manipulated. According to the AFM model, task variables with additive effects on performance are considered to be affecting different stages of processing, whereas variables which interact in their effects are considered to be affecting the same stage. A differentially negative effect on the performance of children with ADHD of a task variable with known effects on a given information-processing stage would be indicative of a specific deficit at the relevant processing stage in the ADHD group. For example, an interaction between a manipulation of stimulus ambiguity and ADHD versus normal group status would be evidence of a specific difficulty at the encoding stage in the ADHD group. With few exceptions [49], studies, reviewed by van der Meere [267], have not succeeded in identifying aberrations in the encoding, memory search, or decision stages of processing in children with ADHD, nor in the domains of orienting, or divided attention [55], nor in attentional capacity [217]. Results indicating a deficiency in the response organization stage have been reported in some studies [28,270], but not replicated in another [49].

The CPT has been widely used to index selective and sustained attention (vigilance) in studies of children with ADHD. On this task, a series of visual stimuli (e.g. numbers, letters, shapes) or auditory stimuli (e.g. tones) is presented, and the subject is required to respond to infrequently occurring target stimuli and to withhold responding to non-target stimuli. Although numerous studies have shown mean differences in overall performance of ADHD and normal control groups on the CPT, which may be considered a gross index of selective attention, relatively few studies have compared groups with respect to sustained attention, ascertained on the basis of performance over time. Of those studies which have compared groups over time, most have found no evidence for a steeper slope of deterioration in the ADHD group [158,164,218,268]. There is, however, recent evidence that deficits in sustained attention are more likely to emerge in ADHD children on tasks with a slow presentation rate (corresponding to a long inter-stimulus interval), possibly because of inadequacy of such stimuli to optimize activation in children with ADHD [269,271]. Differences in presentation rate cannot account for all the discrepancies among studies, however, in that two studies which did report an increased slope of deterioration in children with ADHD used a relatively fast presentation rate (1.5 s) [222,251]. Other differences among studies in CPT task parameters (e.g. stimulus exposure time), subject diagnostic criteria, and co-morbid status may also account for disparate findings.

Contrasting with the many ambiguities and inconsistencies in the attentional literature, there is accruing evidence, recently reviewed by Barkley [10], that children with ADHD have a deficit in inhibitory control which is demonstrable on tasks known to be sensitive to lesions in frontal and prefrontal brain regions. Barkley goes on to elaborate a model wherein this primary difficulty in delaying a response negatively impacts the development of major executive control processes, including: working memory; self-regulation of affect, motivation, and arousal; internalization of speech; and behavioral analysis and synthesis. Together, difficulties in these areas may account for many of the observed symptoms and characteristics of children with ADHD.

An important goal of studies of stimulant drug effects on cognitive performance of children and adolescents with ADHD is to discriminate between generalized effects on state of arousal or activation and effects on specific attentional processes. Most studies have reported MPH-induced increases in overall speed and accuracy on choice reaction time and target detection tasks [122,198,250], but most have failed to find evidence of an interaction between MPH treatment and variables specifically affecting the encoding, memory search, or decision stages of processing in the AFM model [43,48,124,129]. Specific effects on response organization were reported in one study of ADHD children [49], but not in another by the same investigators which was more limited in sample size ($n = 15$) [48]. Increased slowing following errors on the Sternberg task was reported following MPH treatment in one study [129]. This is of particular interest in that a previous study [268] had observed differences between ADHD and normal children in degree of slowing following an error as a function of memory load.

With respect to domains of attention, de Sonneville [49] reported specific positive effects of MPH on focused attention, and Carlson [27] showed MPH increased the allocation of attention to a primary task in a divided attention paradigm. Several studies have demonstrated an enhancement by MPH of sustained attention on the basis of enhanced performance over time on the CPT [48,49,122,123,236]. A recent meta-analysis of 26 studies [141] concluded that MPH reduces errors of omission and commission (false alarms) on the CPT, and enhances d' (the index of perceptual sensitivity, or ability to discriminate target and non-target), but has no significant effect on β (the index of response bias). Sostek [238] reported that D-AMP (0.5 mg/kg) increased d' and β for both ADHD and normal children on a CPT requiring detection of two-digit sequences.

Measurement of event-related potentials (ERPs), particularly the P300 response, has broadened our understanding of stimulant drug effects on cognitive

function. Numerous studies have shown that, concomitant with improvements in accuracy and reaction time, MPH increases the amplitude of the P300 wave on the Sternberg task [124,125], the CPT [43,122,123,140] and visuospatial orienting tasks [163], indicating increased allocation of attentional capacity. In addition, contradicting previous negative findings summarized by Klorman [120], several studies have shown that MPH reduced P300 latency on the CPT [43,124] and other visual feature detection tasks [257], a finding which indicates speeding of stimulus evaluation processes. An independent speeding of the motor response (reaction time (RT) minus P300 latency) was also demonstrated [43].

The effects of MPH on cognitive performance and ERP measures described in the foregoing do not appear to target an anomaly specific to ADHD, in that the same effects have been reported for normal children [172], children not meeting full criteria for ADHD [122,129], and ADHD children with and without aggression or oppositionality [122,129]. Klorman [125] reported that increasing age and MPH had similar effects on cognitive performance, providing further support for a non-specific mechanism of action.

MPH has been shown to enhance inhibitory control in children with ADHD on the 'stop signal task' [254] and the 'go–no-go task' [261].

In summary, neuropsychological research indicates that MPH significantly enhances sustained attention, attentional allocation, as well as the speed and organization of motor response processes and motor inhibitory control. Reduction of P300 latency in a few studies suggests that speeding of stimulus evaluation processes cannot be ruled out. These effects are observed in ADHD and non-ADHD children, and thus do not appear to reflect a mechanism which targets a specific neurobiological deficit in ADHD.

7.2.2. Learning

Effects of MPH on the paired associate learning test (PALT) in children with ADHD have been inconsistent, with some studies reporting enhancement [41,77,194,247] and two others reporting no clear-cut drug effects [57,192]. The small sample size may be responsible for the lack of significant effects in at least one of the two negative studies [192]. Response to MPH on the PALT, however, was not predictive of response to the drug on any other cognitive, academic, or behavioral measure [57]. Rapport and colleagues [275] reported that MPH significantly improved performance on the 'stimulus equivalence paradigm' (SEP) in which the child is required to learn complex visual relationships. Performance on this measure, interestingly, was significantly improved only at the highest dose (20 mg) and was thus less sensitive to the lower drug doses (5.0 and 10.0 mg/kg) than were classroom

measures of observed on-task behavior and academic efficiency. There was no differential effect of MPH seen on learning of the more difficult 'transitive' compared to 'symmetrical' relationships between stimuli on this task.

Improvement in short-term recall on a verbal learning task has been shown for both D-AMP (0.50 mg/kg) [188], and for MPH in a relatively low (10 mg) but not a higher (21 mg) dose [170]. On this task, however, it is not possible to differentiate between drug effects on learning and memory. Evans [69] subsequently used the 'Buschke selective reminding task' to demonstrate linear dose-dependent improvement of 'long-term' memory storage and retrieval variables, but not acquisition, following MPH (0.2, 0.4 and 0.6 mg/kg). Tannock [255] recently demonstrated significant and equivalent improvement of working memory following three doses of MPH (0.3, 0.6 and 0.9 mg/kg) in non-anxious but not in anxious children with ADHD. The only study to examine D-AMP effects in normal children revealed positive effects of 0.5 mg/kg on verbal memory which were largely equivalent to those reported in the same study in children with ADHD [188]. Thus, research to date is inconsistent with respect to MPH effects on acquisition but suggests that it improves long-term and working memory in children with ADHD. It is not clear from limited results to date whether D-AMP facilitates learning, memory, or both.

In 1977, Sprague and Sleator [239] reported a disjunction in dose–response curves of MPH on cognition and behavior, such that performance on a short-term memory task was optimized at a lower dose than were teacher ratings of behavior. Subsequent research, however, [190,233], has not validated the suggestion from this study of a quadratic dose–response curve for cognition, contrasting with a linear dose–response curve for behavior. With the exception of a recent study of inhibitory control [256], the effect of MPH on performance on a variety of cognitive measures—including learning, memory, cognitive impulsivity, cognitive flexibility, and performance on academic tasks—has been either linear improvement with increasing dose up to 1.0 mg/kg, or curvilinear improvement with an asymptote at the highest doses tested; furthermore, with the exception indicated, these curves have not differed significantly from those for behavior, assessed concurrently. A study of time–action curves did yield differences between cognitive and behavioral measures, with effects on behavior (gross motor activity) outlasting those on cognition (RT) [234]. It is important to note that even the highest doses used in these studies correspond to the 'low-dose' range in animal studies—i.e. to stimulant doses which appear to act pre-synaptically and to decrease rather than increase locomotor activity.

Although dose–response curves did not differ significantly and consistently across domains of outcome for the grouped data, the studies reviewed did reveal striking differences between subjects in dose–response curves within a given domain, as well as within-subject variation across domains [57,193,196].

7.3. Normal adults

7.3.1. Attention

Research concerning stimulant drug effects on attentional processes in normal adults have yielded findings largely similar to those in children with or without ADHD. MPH increases overall speed and accuracy, and reduces RT variability on memory search tasks, but does not affect the rate of slowing with increasing memory load, indicating that it does not specifically affect the memory search stage of information processing [16,22,23,73]. As reported in the pediatric research, however, two studies have shown that the enhancing effect of MPH varied with the complexity of the required response, providing evidence for a specific effect of MPH on the response organization stage [73,161].

Examination of ERPs reveals increases in P300 amplitude concomitant with MPH-induced increases in accuracy on memory scanning [73] and continuous performance [121] tasks. As was true in the pediatric studies, effects on P300 latency, which indexes the duration of stimulus evaluation processes, have been inconsistent, with one study reporting a reduction in latency [16] and another finding no change [161].

D-AMP has been shown to reduce errors of omission [188] and commission [93] on the CPT in normal adults. However, the effect of MPH (20 mg) on a non-parametric measure of stimulus discrimination P(A) did not reach significance in a study by Camp-Bruno [24]. Both D-AMP [21,278] and MPH [43,101,242] attenuated the time-related performance decrement on the CPT and other vigilance tasks, indicating an improvement in sustained attention. MPH effects did not interact with cue validity on a covert visual orienting task, however, nor with number of distractors on a visual search task, providing no evidence for drug effects on orienting, or on selective attention, respectively [165]. An adverse effect of MPH (0.15 and 0.30 mg/kg), compared to placebo, on strategic choice behavior, with worse performance on Herrnstein's matching index, has been reported [220].

Several studies have been undertaken with adults to attempt to elucidate the neuropharmacological mechanism of stimulant drug action on cognitive function. Halliday and colleagues [94] applied the Poisson–Erlang model [174] of choice reaction time to differentiate between drug effects on processing time (time devoted to the cognitive operations necessary to generate a correct response) and distraction time (time devoted to

all other activities). They demonstrated that D-AMP (10 mg) selectively reduced processing time in the hard response condition on the stimulus evaluation response selection (SERS) information-processing task, indicating a specific effect on motor activation (as opposed to stimulus evaluation) processes. Cochran and colleagues [39] arrived at a similar conclusion in their study which employed a warned reaction time task with randomized foreperiods to differentiate between D-AMP effects on arousal and activation. The authors postulated that a differential effect of the drug on trials with a short foreperiod would indicate a greater effect on arousal since performance on these trials is largely determined by the alerting response to the warning stimulus, whereas a greater effect on trials with a long foreperiod reveals a greater drug impact on activation given that preparation time (and hence activation requirement) is greater. Results showed that the facilitating effect of D-AMP (20 mg), as well as the impairment produced by sleep deprivation, increased with the length of the foreperiod, indicating predominant effects on activation by both of these interventions. Involvement of the DA system, implied in the facilitation of activation [264] has received support in other research with adults. Clark and colleagues [36] reported that MPH reversed the negative effects of the DA antagonist droperidol on divided and focused attention on a dichotic listening task. Furthermore, L-dopa has been found to improve effortful (but not automatic) processing in normal elderly adults [162]. A role for serotonin was suggested in the finding that the 5-HT-3 receptor antagonist, ondansetron, attenuated the facilitative effects of D-AMP on psychomotor performance [228].

7.3.2. Learning and memory

The effects of D-AMP on learning and memory in adults have been explored in numerous studies using word list and PALTs. Early studies yielded variable effects on acquisition, with reports of no effect [126], impairment at a high dose (15 mg) [19], and a facilitative effect on learning of non-competitive but not competitive word lists [279]. Hurst and colleagues [110] reported that pre-training D-AMP (0.2 mg/kg) improved retention 1 week post-training in the absence of effects on initial acquisition. Studies by Rapoport [188] found that pre-training administration of 0.25 or 0.5 mg/kg facilitated short-term (10 min) recall. Most recently, Soetens et al. [230] provided compelling evidence that D-AMP facilitates memory consolidation processes even in the absence of direct effects on initial acquisition. In a series of five experiments, these investigators demonstrated that D-AMP (10 mg) whether given orally 1 h before word list presentation or injected immediately afterward, such that it is active within 1 h after learning, improves retention at post-training intervals of 1 h, and 1, 2 and 3 days.

Little research has been done to examine and differentiate among effects of MPH on acquisition, memory consolidation, and retrieval processes. Wetzel and colleagues [282] reported an adverse effect of MPH (0.5 mg/kg, i.v.), infused 15 min before training, on word list acquisition. There was no effect of infusion within 1 h after training, nor any effect at all of lower doses (0.1 or 0.25 mg/kg). Retention at 24 h was not affected in any condition. More recently, Camp-Bruno et al. [24] reported a positive effect of MPH (20 mg, p.o.) on the Buschke Selective Reminding Test, sum recall index (a measure of acquisition), administered 2 h post-drug. In this same study, there was no effect on immediate or delayed free recall of other word lists presented only once. The discrepancy in results of these studies may again be due to the use of a dose in the study by Wetzel [282] which, given the i.v. mode of administration, was excessively high.

In conclusion, research on information-processing in normal adults clearly indicates that MPH and D-AMP enhance motor response, but not stimulus evaluation, processes. Both drugs also improved sustained, but not selective, attention. Research with D-AMP has yielded inconsistent effects on acquisition and facilitation of memory consolidation, whereas limited research with MPH reveals positive effects on acquisition, but not retention.

8. Genetic studies

Research in molecular genetics is beginning to yield data which supports the hypothesis that dopaminergic functioning is aberrant in ADHD. Several recently completed studies [42,78,276] have reported an association between ADHD and the 480-base pair DAT1 allele for the DA transporter. There is no indication currently, however, as to whether or in what way this polymorphism may affect DA transporter function. Recent research [132,249] also suggests increases in prevalence of the 7-repeat allele for the D-4 gene, which has been associated with novelty-seeking behavior in some studies of adults.

9. Brain imaging studies

New techniques of brain imaging in animal and human studies provides a 'window' which can potentially reveal exactly which sites in the brain are targeted by psychostimulants and other drugs.

9.1. Animals

Porrino and Lucignani [179] reported distinctly different patterns of local cerebral glucose utilization (LCGU) following acute doses of MPH in the mesolimbic and nigrostriatal dopaminergic systems in rats using the autoradiographic [^{14}C]deoxyglucose technique. In the nucleus accumbens, increases in LCGU were seen following the lower doses which also increased locomotor activity (1.25–5.0 mg/kg). By contrast, LCGU values were not higher than control levels following 15.0 mg/kg, which induced marked stereotypy. In the extrapyramidal system, however, particularly the globus pallidus, entopeduncular nucleus and substantia nigra, increases in LCGU were apparent with increasing dosage up to and including 15.0 mg/kg. Interestingly, increases were not seen in the medial PFC at any dose, and were seen in the frontal cortex only at 1.25 mg/kg. Parallel results were reported for D-AMP, with increases in LCGU confined mainly to the nucleus accumbens following the lowest doses tested (0.2 and 0.5 mg/kg) [183], and increasing metabolic activity in the nigrostriatal region with increasing dose. These results suggest that the mesolimbic system is more important in mediating the therapeutic effects seen clinically, which occur at doses at the lower end of the ranges tested.

Tsai and colleagues [263] recently used the LCGU method to assess metabolic changes in rats following chronic D-AMP treatment (0.0, 1.0, 5.0 or 10 mg/kg for 14 days). Significant increases in LCGU activity were found in the nucleus accumbens and lateral habenular nucleus, but, unexpectedly, not in the nigrostriatal region, despite the finding that the chronically treated animals showed an intensive stereotypy response to a challenge dose of 5 mg/kg D-AMP.

9.2. Humans

9.2.1. ADHD versus normal comparison

The results of studies of regional cerebral blood flow (rCBF) and neuroimaging comparing human subjects with ADHD and normal controls have been inconsistent, both within and across laboratories, with respect to localization of differences in perfusion and metabolism. The most consistent finding across three CBF studies conducted by Lou [142,143] of small overlapping samples of children with ADHD having significant neurodevelopmental co-morbidity, was decreased perfusion in the right striatal region. MRI studies by Hynd and colleagues [111], also using small samples of children with ADHD, found reduced volume in the right frontal cortex of patients, such that the normal asymmetry (R > L) was lost in the patients. The volume of the corpus callosum and the left head of the caudate was also reduced in the patients. Zametkin and colleagues [289] used PET with [^{18}F]fluorodeoxyglucose to study 60 brain regions in 25 adult subjects with ADHD and found significantly reduced metabolism in frontal and subcortical (thalamus, caudate, hippocampus and

cingulate) regions on the right. When normalized (divided by global metabolism values), the results indicated that metabolic rates of four regions in the left premotor and somatosensory areas were reduced. These findings were not replicated in a subsequent study of teenagers with ADHD [290].

The results of the most extensive study in this area were recently published by Castellanos and colleagues, also at NIMH, who compared the anatomic brain MRIs for 57 boys with ADHD and 55 matched normal controls [32]. Subjects with ADHD had a significantly smaller right caudate than did controls, with loss of the normal right > left asymmetry. In addition, ADHD subjects had a smaller right anterior frontal region, smaller right globus pallidus, smaller cerebellum, reversal of the normal lateral ventricular asymmetry, and 4.7% smaller total cerebral volume. The functional significance of the anatomical differences in this sample was highlighted in the finding of significant (negative) correlations between performance on inhibitory tasks and the volume (predominantly on the right) of three brain regions which differentiated the normal from ADHD groups: the PFC, caudate and globus pallidus [29].

Ernst [66] recently reported highly elevated levels of [^{18}F]fluorodopa in DA neurons on PET scan of the substantia nigra and VTA of adolescents with ADHD. Furthermore, the level of [^{18}F]fluorodopa was positively correlated with severity of ADHD symptoms. These findings, which are suggestive of increased pre-synaptic dopaminergic activity in ADHD, may be related to recent reports by Castellanos [30] of a positive correlation between CSF levels of homovanillic acid (HVA), the primary metabolite of DA, and degree of hyperactivity in boys with ADHD. This finding was replicated in a subsequent study [31], which reported, in addition, that high CSF HVA was a significant predictor of a positive response to stimulant medication.

9.2.2. Effects of stimulant drugs

Lou and colleagues [142,143] reported that a treatment dose of MPH (10–30 mg) increased perfusion in the striatal region. PET has been used to study the effects of stimulant drugs in adults with ADHD while subjects performed an auditory CPT. The first study [148] reported no effects on global metabolism following a single acute dose of D-AMP (0.25 mg/kg) or a single acute dose of MPH (0.35 mg/kg). Changes (increases or decreases) were reported in seven of 60 regions tested following D-AMP, including increases in the right caudate and right thalamus. MPH produced changes in five of 60 regions, including increases in the left posterior frontal and left parietal regions. There was only one region of change in common for the two drugs: in the anterior medial frontal region, activity increased by 3.4% following D-AMP, but decreased by

9% following MPH. These results, if replicated, suggest different central mechanisms of action for the two stimulants. A subsequent study [149] of the effects of chronic stimulant treatment (for a minimum of 6 weeks) with clinically titrated doses of D-AMP and MPH found no effects on metabolism following D-AMP treatment, and changes in only two of 60 brain regions sampled following MPH treatment. A recent PET study of normal adult volunteers reported maximal binding of carbon-labeled MPH in the striatum, with low levels in the cortex and cerebellum [274]. Finally, no effects on global or regional metabolic rates were reported following acute i.v. infusion of 0.15 mg/kg D-AMP in adults with ADHD [65].

A recent study [150] used PET to study the effects of D-AMP (0.25 mg/kg) on rCBF in normal adults performing two abstract reasoning tasks: the Wisconsin card sorting test (WCST), a test of executive control which is sensitive to the functional status of the dorsolateral PFC; and the Ravens progressive matrices (RPM), a test of non-verbal intelligence linked to posterior cortical systems. Results showed that D-AMP increased rCBF in the PFC (specifically, the superior portion of the left inferior frontal gyrus) during the WCST and decreased it during RPM. In the hippocampus, drug effects were reversed in that rCBF was increased during RPM and decreased during WCST. These results illustrated that D-AMP focused neural activation in those regions which mediate performance of specific cognitive tasks, a finding which may underlie its effectiveness in ADHD as well.

10. Animal models

Several well-developed models of ADHD have been generated in animals by neurotoxic lesions of dopaminergic nerve endings, and by selective breeding. Shaywitz [225,226] and others [144] produced rats with high locomotor activity and deficits in avoidance learning by administering intracisternal injections of 6-OH-DA (plus desipramine (DMI), to protect noradrenergic endings) to pups. Injections of D-AMP or MPH in doses which increased the activity level of normal rats reduced locomotor activity and reversed the behavioral deficits of the lesioned rats.

In a series of studies by Le Moal and colleagues [135,136], more specific dopaminergic lesions of the A10 neuron group in the VTA of adult rats produced animals characterized by: (1) increased locomotor activity; (2) deficits in behavioral suppression; (3) disappearance of behavioral patterns essential to survival of the individual or species (e.g. social, maternal); (4) deficits in active avoidance learning and responding on continuous or fixed-interval reinforcement schedules; (5) deficits in intracranial self-stimulation and self-adminis-

tration of stimulant drugs; and (6) profound deficits in attentional and representational cognitive processes as measured by delayed alternation tasks. The hyperactivity and attentional deficits were correlated with decreases in DA in the anteromedian frontal cortex and the nucleus accumbens. Chronic D-AMP injections (e.g. twice daily for 43 days), which increased activity in normal rats, brought about a progressive decrease in hyperactivity of the lesioned rats.

It should be noted that although these two models appear to reproduce some of the major behavioral characteristics of ADHD, the response to stimulants is not comparable to that seen in the clinical disorder in that: (a) the effects in normal and lesioned individuals were dichotomous; and (b) D-AMP treatment produced a lasting reversal of the deficits in the model by Le Moal.

Sagvolden and others developed the spontaneously hypertensive rat (SHR) strain as a model of ADHD. Studies have shown that this strain has discrimination deficits, locomotor hyperactivity, increased behavioral variability, and increased level of bar-pressing during extinction on a FI reinforcement schedule [212,213] compared to the normal (WKY) progenitor strain. On a variable interval reinforcement schedule, fewer reinforcers per minute were required to maintain high levels of responding in SHR than in WKY rats, interpreted as indicating increased sensitivity to immediate reinforcement in the SHR rats, and paralleling postulations by Douglas [56] concerning the nature of the reward dysfunction in ADHD. In addition, SHR rats exhibited a more intense 'scallop' or steeper delay-of-reinforcement gradient on a FI reinforcement schedule [211], characterized by an increased rate of response in all segments of the interval after the first. D-AMP and MPH treatments flattened the response gradient in both WKY and SHR rats by increasing the response rate early in the interval and decreasing the response rate later in the interval [211], with a more pronounced drug effect in the WKY rats. The authors concluded that the effect of the stimulants was to decrease sensitivity to immediate reinforcers and increase sensitivity to delayed reinforcers. When considered in terms of the matching law, the overall effect of MPH was to increase c, which is the reinforcement rate required to maintain a half-maximal response rate. Thus, contrary to the results of studies showing drug-induced enhancement of reward processes in animals, the effect of the stimulant in this study was to reduce reinforcement efficacy.

Aberrations in dopaminergic function have been described in the SHR strain, including reduced release of DA in PFC and caudate-putamen with evidence of increased efficacy of DA autoreceptors in the nucleus accumbens [207], and decreased DA and 5-HT turnover in the substantia nigra, VTA and frontal cortex [50,266]. Several discrepant reports of increased DA

turnover [154] and enhanced DA levels in the frontal cortex of SHR rats [272] have also appeared, however, along with reports of enhanced D1- and D2-receptor binding [119].

Sadile and colleagues [208] produced the Naples high excitability (NHE) strain by selectively breeding rats on the basis of high frequency of corner crossings and rearings upon exposure to spatial novelty in a Làt-maze. The strain is characterized by reduced behavioral habituation to spatial novelty, but no differences from normals in 24-h spontaneous locomotor activity, which limits its comparability to ADHD [182]. It was also reported recently that NHE and SHR rats showed constant duration of rearing over 10 min after placement in a Làt-maze, compared to the increasing duration seen in normal rats, interpreted by the authors as indicating reduced attention in the NHE rats [209]. However, rearing duration has not yet been validated as an index of 'attention' in this animal model.

11. Effects in ADHD of non-stimulant drugs affecting specific neurotransmitter systems

Given that the psychostimulants have, as described, numerous effects on both the DA and NE neurotransmitter systems, comparison with drugs having somewhat more delimited effects may be helpful in parsing out therapeutic mechanisms of action [288]. In small samples, the DA agonists, piribedil and amantadine, were not found to be clinically effective [288], possibly because the dosages were too high. The DA antagonist, haloperidol [281] was moderately effective in reducing global ratings of hyperactivity although it did not improve cognitive function. The possibility that the drug's effects on behavior were mediated by increased sedation cannot, therefore, be ruled out. An alternative possibility suggested by haloperidol's positive effects on behavior is that stimulants may be acting to inhibit DA neurotransmission in ADHD, as will be further discussed. Studies which have combined MPH with a neuroleptic (DA antagonist) thus far provide inconsistent support at best for such an hypothesis, however. Whereas Gittelman [80] and Weizman [280] reported that thioridazine and propericazine, respectively, enhanced the positive effects of MPH on behavior ratings, Levy [137] found that haloperidol blocked the facilitative effects of MPH on a cognitive test battery which included the CPT. In normal adults, the DA antagonist droperidol exerted an adverse effect on divided and focused attention on a dichotic auditory attention task [36]. This negative effect was reversed by MPH, which had no effect when administered alone.

Among drugs which act primarily (although not exclusively) upon the NE system, the tricyclics, which block reuptake, are moderately effective, but less so

than the stimulants in treating ADHD [175]. Clonidine reduced parent- and teacher-rated hyperactivity and conduct problems in ADHD children [108], but had no effect on a neuromaturational test battery. Furthermore, an open pilot study found clonidine to be less effective than MPH on behavioral measures [106]. Open-label clinical trials have recently yielded behavioral improvement [33,103,109], and improvement on the CPT [33] with guanfacine, a specific agonist at the α-2a receptor, which lacks the sedative and hypotensive side effects due to clonidine's actions at the α-2b and α-2c receptors, respectively. Direct comparisons between guanfacine and the psychostimulants have not yet been conducted, however.

In contrast to indications thus far of only moderate effectiveness of NE-selective agents, the MAO-A and MAO-A + B inhibitors, clorgyline and tranylcypromine, respectively, which facilitate the action of both DA and NE, were 'clinically indistinguishable' from D-AMP in improving parent and teacher ratings of behavior and enhancing performance on the CPT [287]. The immediate therapeutic effect of the MAO inhibitors in ADHD, contrasting with the delayed effect in the treatment of depression, suggested different mechanisms of action in the two disorders.

Taken together, these studies suggest that dopaminergic and noradrenergic mediation each contribute to the therapeutic efficacy of the stimulants, and that efficacy is maximal for those drugs which simultaneously affect both systems. Clinical studies of the effects of the tricyclics compared to stimulants, in children with ADHD, reviewed by Rapport [195], have attempted to discriminate the cognitive functions mediated by each neurotransmitter. Four studies comparing the tricyclics DMI or amitriptyline to placebo found no effect of these drugs on cognitive function or, in one study, an adverse effect on short-term memory. Two of three studies comparing tricyclics to psychostimulants on the CPT reported superior effects of MPH on CPT omission errors; commission errors were either unaffected or reduced equivalently by each drug. Effects on motor and perceptual performance were inconclusive, with three studies reporting a superior effect for the stimulants and three others favoring the tricyclics.

Rapport [195] studied the effects of DMI and MPH separately and together on cognitive function in hospitalized children with mixed features of ADHD and depressive disorder. The results revealed that only MPH improved vigilance (CPT errors of omission). The lack of effectiveness of the combination of DMI with MPH on CPT omission errors, furthermore, suggested a blocking effect of DMI. MPH was superior to DMI in enhancing PALT. On tasks requiring inhibitory control (Matching Familiar Figures Test) or more complex learning (SEP), the combination of drugs was superior to any other condition. A tentative conclusion from

these findings was that DA was more important than NE in mediating basic attentional processes and vigilance, whereas NE was involved in mediating performance on tasks requiring both inhibitory control and more complex problem-solving abilities.

The possible involvement of serotonin in mediating the positive effects of the stimulants in ADHD was assessed by Donnelly [54], who found that fenfluramine had no positive effects on behavior in ADHD children in either a low (0.6 mg/kg per day) or high (2.0 mg/kg per day) dosage.

12. Discussion and implications

Integration of the basic neuropharmacology of the psychostimulants with the results of pre-clinical and clinical studies of their effects on behavior, cognition, electrophysiology, brain imaging, and neurochemistry suggests likely or possible modes of therapeutic action of these drugs in ADHD with respect to the following questions.

12.1. Which neurotransmitters?

Several sources of evidence lead to the conclusion that effects on both NE and DA are important to psychostimulant efficacy. It is well-established that the stimulants potentiate the actions of both NE and DA in the synapse and, specifically, alter the activity of the nigrostriatal and mesocorticolimbic dopaminergic systems, as well as noradrenergic projections from the LC to the cortex. Clinical trials, furthermore, reveal that whereas agonists and antagonists with selective effects on either the NE or DA systems may produce modest improvement in behavior or cognition in ADHD, the drugs which are maximally effective are those which, like the stimulants, exert effects on both neurotransmitters.

Results of information-processing studies in normal and clinical populations suggest psychostimulants primarily enhance motor activation, believed to be mediated by DA. However, given some reports of MPH-induced changes in P300 latency, effects on stimulus evaluation processes, mediated by NE, cannot yet be completely ruled out. Dopaminergic projections from the nucleus accumbens are known to mediate stimulant effects on reinforcement processes and stimulus control of behavior in animals, as well as the rate-dependent effects, which may account, at least in part, for the reduction in activity level in ADHD.

Effects on NE are more directly suggested by the finding that D-AMP inhibits the spontaneous activity of neural projections from the LC to the PFC, which are known to mediate processes involving learning, selective and sustained attention, as well as working mem-

ory, and response to distraction and delay. Increasing evidence for involvement of both DA and NE in modulating the activity of the PFC lends further support to the hypothesis that both are involved in mediating the effects of the stimulants on cognitive function.

12.2. Facilitation or inhibition?

12.2.1. Dopamine

Whereas most recent theories of stimulant drug effectiveness postulate involvement of both NE and DA, our understanding of specific cellular mechanisms is in its infancy. The immediate onset of therapeutic effect and the lack of tolerance suggests that effects in ADHD are not mediated by changes in sensitivity of pre- or post-synaptic receptors. Whether the acute phasic effects of the drug result from drug-induced catecholamine stimulation of pre- or post-synaptic receptors is unresolved, however. In 1984, Solanto [231,232] became the first to suggest that D-AMP and MPH may act therapeutically by stimulating inhibitory pre-synaptic dopaminergic autoreceptors, thereby reducing DA neurotransmission. This hypothesis was based on the biphasic effects of D-AMP observed in animal studies, in which autoreceptor-stimulating doses reduce activity level, higher post-synaptically active doses increase activity level, and very high doses increase stereotypy with a concomitant reduction of locomotor activity and constriction of attentional focus.

Solanto [232] empirically tested the 'autoreceptor hypothesis' against the alternate hypothesis that the beneficial effects of stimulant medications in children are commensurate with the increase in stereotypy and reduction in locomotor activity seen in animals at the very high doses known to stimulate post-synaptic receptors. If clinically effective doses correspond to those which generate stereotypy, then 'subclinical' doses were predicted to produce the increase in locomotor activity seen in animals at intermediate doses. Results of this study revealed that a subclinical dose of MPH (0.1 mg/kg) significantly reduced activity level in children with ADHD, suggesting that the clinically effective dosage range corresponds to the lower 'autoreceptor-sensitive' range of the dose–response curve derived from animal studies. In addition, subsequent research on divergent thinking, creativity, and other higher-order functions, has failed to yield support for the idea that the positive effects of stimulants are mediated by increases in cognitive constriction, perseveration, or stereotypy [58,235,253].

There are a number of challenges to the hypothesis of pre-synaptically mediated stimulant medication effects which will have to be addressed and resolved in future research. First, the hazards in generalizing from dose–response effects on locomotor activity in animals to drug effects on activity level in children are well-acknowledged. Secondly, the adverse or non-facilitative cognitive effects of DA antagonists such as droperidol and the neuroleptic drugs, despite apparent positive effects on behavior by the latter, are not consistent with a model of inhibitory therapeutic effects of the stimulants on dopaminergic transmission. However, it may be that dosages in these studies were too high. The positive effects of the MAO inhibitors, which presumably prolong catecholamine effects at the post-synaptic receptor, may at first also appear to be incompatible with an autoreceptor mechanism of action. Blier and de Montigny [12] have postulated, however, that the MAO-induced immediate increase in catecholamine neurotransmission is quickly followed by stimulation of autoreceptors and an accompanying reduction in neuronal firing. The delayed onset of the anti-depressant effect, not seen in the treatment of ADHD, is believed to correspond to the period required to produce desensitization of the autoreceptors with resulting enhancement of catecholamine output.

The development of animal models of ADHD by neurotoxic depletion of DA [136,225] poses another challenge to the autoreceptor hypothesis, as do reports of decreased dopaminergic activity in the SHR model of ADHD. However, other animal research has demonstrated that infusions of DA directly into the nucleus accumbens of monkeys increased locomotor activity, an effect which was blocked by administration of the neuroleptics sulpiride or fluphenazine [11]. More recently, it has been shown that the behavior of mice with genetically engineered knockout of the DA transporter, and consequently markedly increased DA in the extracellular space, is also characterized by extremely high levels of spontaneous locomotor activity [79]. It may be that positive or negative deviations of DA function (i.e. excess or depletion) can produce increased motor activity, at least in animal models. Recent clinical research demonstrating positive correlations between severity of ADHD symptoms and levels of pre-synaptic [^{18}F]fluorodopa on PET [66], as well as HVA in the CSF [30,31] suggests that the pathophysiology of ADHD involves elevated dopaminergic activity.

12.2.2. Norepinephrine

The effects of the psychostimulants on NE neurotransmission have been less well studied at the neuronal level than is the case for DA. However, indirect evidence admits of the possibility of relative noradrenergic overactivity in ADHD and inhibitory therapeutic effects of the stimulants. In studies with monkeys, high tonic levels of activity were associated with behavioral agitation and worse vigilance performance than were more moderate levels. As described, both MPH and D-AMP have been shown to produce a significant reduction in firing of LC neurons. Furthermore, as discussed, the lower doses of D-AMP (0.25–0.50 mg/kg)

often maximally improve attention and learning in animal and human adult studies, whereas higher doses are more likely to impair performance.

As reviewed, it has been shown repeatedly in both human and animal studies that pre-synaptically effective doses of the adrenoceptor agonist clonidine produce impairment of cognitive performance, whereas post-synaptic doses improve performance. It is notable, however, that these studies were all conducted with normal or NE-depleted subjects. If ADHD is characterized by relative noradrenergic over-arousal, as suggested by the studies of LC activity, it may be remediable by pre-synaptically acting doses of clonidine. Although dose–response curves in adults and children are not directly comparable due to developmental differences in pharmacodynamics, the behaviorally effective dosage of 1.0–1.25 μg/kg b.i.d. in children with ADHD reported by Hunt [108] would appear to best approximate the 'pre-synaptic doses' of 200 μg, or approximately 2.8 μg/kg, which produced impairment in adult studies. Inferences as to mechanisms, however, are hampered by a dearth of data with respect to the dose–response effects of clonidine and guanfacine on the cognitive functioning of children with ADHD.

Acknowledging that urinary catecholamine levels may not correlate well with central catecholamine activity, it is nonetheless interesting that several studies have shown that stimulant treatment of children with ADHD reduces, rather than increases, urinary excretion of MHPG, the major metabolite of NE [288], which would be expected given an inhibitory effect of stimulants on noradrenergic activity. Furthermore, clinical improvement on DMI is significantly correlated with the decrease in urinary MHPG [189].

Other investigators have also proposed that the pathophysiology of ADHD involves 'overdrive' of the LC, with excessive NE release leading to reduced capacity of the PFC to respond to phasic stimuli [152,157,177]. McCracken, Pliszka and colleagues, however, suggest that stimulants correct this abnormality by enhancing release of epinephrine in the periphery, thereby inhibiting LC activity via sensory afferents [152,177].

12.3. Which brain region(s)?

Results of clinical and pre-clinical neuroimaging, neuropharmacological, and neurophysiological research are converging to implicate a primary dysfunction of PFC, caudate, and globus pallidus in ADHD, which recent MRI studies indicate is lateralized to the right side. While a right-hemisphere dysfunction is consistent with findings of left-sided hemispatial neglect on a letter cancellation task [273], and left-sided abnormalities on a spatially cued orienting task [248], other neuropsy-

chological studies highlight a disturbance of motor response processes, which are believed to be mediated by DA and localized primarily to the left hemisphere. The case for right-sided dysfunction was recently strengthened, however, by the finding of significant (negative) correlations between performance on tests of inhibitory control and volume of the anterior frontal region, caudate and the globus pallidus on the right [29].

Research suggests that the psychostimulants do not target the disease locus or deficit(s) which are specific to ADHD, but rather act in a compensatory manner via a CNS mechanism which obtains in normal as well as disordered individuals. It may be, for example, that by reducing excessive stimulation of α-1 or D-1 receptors via ascending noradrenergic or dopaminergic projections, the stimulants optimize the functioning of an otherwise compromised prefrontal region in ADHD.

12.4. Implications for pre-clinical research

A review of drug effects in individuals with ADHD indicates that animal models of ADHD which are most representative of the clinical disorder will be characterized by the following: (1) elevated 24-h spontaneous locomotor activity; (2) deficits in inhibitory control (e.g. in passive avoidance, extinction, and go–no-go paradigms); (3) deficits in stimulus control of behavior; (4) remediation of the foregoing deficits by low-dose D-AMP (0.5 mg/kg or less) administration; (5) a response to stimulants which is behaviorally undifferentiable from that seen in normal animals; (6) absence of tolerance to stimulant drug effects; (7) absence of differences between acute and chronic effects of drug treatment on specific behavioral processes, including absence of long-term drug-induced behavioral remediation; (8) rate-dependent effects of stimulants on spontaneous motor activity and schedule-induced responding; and (9) absence of biological anomalies not characteristic of ADHD children (e.g. hypertension). Further clinical research is necessary to elucidate the extent to which a specific reward dysfunction characterizes ADHD, the impact of stimulant drugs on those reward processes, and the possibility of amphetamine-induced behavioral sensitization in the clinical disorder.

There appears to be a dearth of studies comparing pre-synaptic and post-synaptic effects of stimulants as these may be relevant to ADHD. Selective stimulation of pre- versus post-synaptic receptors via dosage titration, or use of receptor-selective drugs, with measurement of concomitant effects on locomotor activity, motor activation, vigilance, inhibitory control, memory, and response to reinforcement would seem to be necessary to fully test any hypotheses concerning facilitative versus inhibitory effects of the stimulants on the catecholamines. Furthermore, as described more fully be-

low, a co-ordinated program of pre-clinical and clinical research on drug effects, utilizing comparable doses and parallel cognitive and behavioral response measures, would optimize further research on mechanisms of therapeutic drug action in ADHD.

12.5. Implications for clinical research

The review of pre-clinical research suggested a number of fruitful directions for research in human subjects. The first would appear to be the increased use of paradigms measuring response to delay, inhibitory control, and vigilance which have been shown to be sensitive to specific brain lesions in animal work. Among these are the delayed alternation paradigm [2] and other tests of working memory, which are sensitive to prefrontal lesions. Secondly, questions concerning pre- versus post-synaptic effects of stimulants, as well as effects on specific neurotransmitters and receptor subtypes can best be addressed by systematic and co-ordinated clinical and pre-clinical testing of a host of newly developed drugs with more specific agonist, antagonist, receptor subtype, as well as pre- versus post-synaptic effects. Among such drugs are specific DA autoreceptor agonists being developed for the treatment of schizophrenia [224], which, given the hypotheses propounded above, may have potential for the treatment of ADHD as well. In this context, it is notable that Sallee [214] recently reported that pergolide, a selective D-2-autoreceptor agonist, was mildly effective in reducing activity level and improving clinical global impression ratings in individuals with ADHD plus Tourette's. In addition to comparison with psychostimulants, it will be useful to ascertain whether the combination of any new drug with a psychostimulant has additive, synergistic, or blocking effects. Thirdly, despite largely equivalent group response of children with ADHD to D-AMP and MPH, the preferential response of some individuals to one drug or the other, as well as evidence of differences between the drugs in effects on cellular processes, points to corresponding differences in central mechanisms of action. More intensive study and comparison of preferential responders to specific stimulants or to other catecholaminergic agents with respect to their neuroimaging, neurochemical, neuropsychological, behavioral, and genetic characteristics, may help to elucidate stimulant mechanisms and delineate meaningful subtypes of ADHD. Fourth, despite striking evidence of facilitatory effects of stimulant drugs on reward and memory processes in animal and human studies, as well as the possibility of disturbed reward sensitivity in children with ADHD, these areas are relatively unexplored in clinical research in ADHD. Finally, rapid developments in two areas—molecular genetics, and functional magnetic resonance imaging (which permits identification of brain regions which are active during specific cognitive tasks or behaviors)—may revolutionize our ability to identify the neurobiological deficit(s) in ADHD and the compensatory mechanisms of stimulant drug action.

Continuing dialogue between pre-clinical and clinical researchers would appear to be crucial to a comprehensive understanding of the mechanisms of action of psychostimulants and other drugs in ADHD and, potentially, to the development of more effective therapeutic agents.

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